

## WE CLAIM:

1. A method of producing a population from pancreatic tissue enriched for human pancreatic stem cells, progenitors, or a combination thereof, comprising:
  - 5 a) contacting pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells with a monoclonal antibody that binds CD133 or CD49f; and
  - b) selecting said pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells that bind to the  
10 monoclonal antibody;wherein the selected cells are enriched for human pancreatic stem cells, progenitors, or a combination thereof.
2. The method of claim 1, wherein the population containing pancreatic stem/progenitor  
15 cells, is obtained from a suspension culture or an adherent culture.
3. The method of claim 1, wherein the population containing pancreatic stem/progenitor cells, is obtained from any tissue which gives rise to pancreatic tissue.
- 20 4. The method of claim 1, wherein the population containing pancreatic stem/progenitor cells is obtained from primary gastrointestinal tissue or gastrointestinal derived explant.
5. The method of claim 1, further comprising the steps of further enriching a population from pancreatic or gastrointestinal tissue for pancreatic stem cells, progenitors, or  
25 combinations thereof by
  - c) contacting the selected cells with a second monoclonal antibody that binds CD34 or CD45; and
  - d) removing those cells that are CD34<sup>+</sup> or CD45<sup>+</sup>,wherein the remaining cells in the population are CD34<sup>-</sup> or CD45<sup>-</sup> and are enriched for  
30 pancreatic stem cells, progenitors, or combinations thereof.

6. The method of claim 1, wherein the pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells are contacted with an anti-CD34 monoclonal antibody or an anti-CD45 monoclonal antibody, and wherein the bound cells are removed prior to the contacting of step a).

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7. A method for producing a population enriched for human pancreatic stem cells, progenitors, or a combination thereof, comprising selecting from a population of pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells for those cells that are CD133<sup>+</sup>, or CD49f<sup>+</sup>, or CD133<sup>+</sup>CD49f<sup>+</sup>.

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8. The method of claim 7, wherein said selection is accomplished by contacting the population of cells with an anti-CD133 antibody such as monoclonal antibody AC133 and removing those cells that do not bind to the anti-CD133 antibody.

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9. The method of claim 7, wherein said selection is accomplished by contacting the population of cells with an anti-CD49f antibody selected from the group consisting of monoclonal antibody GoH3 and monoclonal antibody 4F10 and removing those cells that do not bind to the anti-CD49f antibody.

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10. The method of claims 8 or 9, further comprising the step of further enriching the population obtained from pancreatic tissue for pancreatic stem cells, progenitors, or combinations thereof by removing the cells that are CD34<sup>+</sup> from the remaining population of pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells.

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11. The method of claim 10, further comprising the step of further enriching the population by removing the cells that bind to a monoclonal antibody that recognizes CD34.

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12. The method of claims 8 or 9, further comprising the step of further enriching the population obtained from pancreatic tissue for pancreatic stem cells, progenitors, or combinations thereof by removing the cells that are CD45<sup>+</sup> from the remaining

population of pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells.

13. The method of claim 12, further comprising the step of further enriching the population  
5 by removing the cells that bind to a monoclonal antibody that recognizes CD45.

14. A method for enriching from a population of pancreatic tissue, pancreatic cells,  
pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells  
for the populations of pancreatic stem cell or progenitor fractions, comprising selecting  
10 from the pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary  
gastrointestinal tissue or gastrointestinal-derived cells for cells that express CD133 by  
binding to monoclonal antibody AC133, wherein the selected cells are enriched in the  
fraction of pancreatic stem cells as compared with the population of pancreatic tissue,  
pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or  
15 gastrointestinal-derived cells.

15. A method for enriching a population of pancreatic tissue, pancreatic cells, pancreatic-  
derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells for the  
populations of pancreatic stem cell or progenitor cell fractions, comprising selecting from  
20 the pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal  
tissue or gastrointestinal-derived cells for cells that express CD49f by binding to  
monoclonal antibody GoH3 or monoclonal antibody 4F10, wherein the selected cells are  
enriched in the fraction of pancreatic stem cells as compared with the population of  
pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal  
25 tissue or gastrointestinal-derived cells.

16. The method of claims 14 or 15, further comprising the step of further enriching for the  
fraction of pancreatic stem cells from primary tissues by removing the cells that are  
CD34<sup>+</sup>.

17. The method of claims 14 or 15, further comprising the step of further enriching for the fraction of pancreatic stem cells from primary tissues by removing the cells that are CD45<sup>+</sup>.
- 5 18. The method of claims 14 or 15, further comprising the step of further enriching for the fraction of pancreatic stem cells from primary tissues by removing the cells that are CD34<sup>+</sup> and CD45<sup>+</sup>.
- 10 19. A method for isolating a pancreatic stem cell from primary pancreatic tissues, comprising:
- a) selecting from a population of pancreatic cells, pancreatic-derived cells, or gastrointestinal-derived cells for cells that are CD133<sup>+</sup>, or CD49f<sup>+</sup>, or CD133<sup>+</sup>CD49f<sup>+</sup>;
  - b) removing the cells that are CD34<sup>+</sup>, CD45<sup>+</sup>, or CD34<sup>+</sup>CD45<sup>+</sup>, wherein the  
15 remaining cells are CD34<sup>-</sup>, CD45<sup>-</sup>, or CD34<sup>-</sup>CD45<sup>-</sup>;
  - c) introducing the cells remaining after step b) to a serum-free culture medium containing one or more growth factors; and
  - d) proliferating the remaining cells in the culture medium.
- 20 20. A method for producing a population enriched for human pancreatic stem cells, progenitors, or combinations thereof comprising selecting from pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells for cells that are CD133<sup>+</sup> and bind to an anti-CD133 antibody such as monoclonal antibody AC133, to produce a population enriched for  
25 pancreatic stem cells, progenitors, or combinations thereof, wherein the selecting is by attachment to and disattachment from solid phase.
- 30 21. A method for producing a population enriched for human pancreatic stem cells, progenitors, or combinations thereof comprising selecting from pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells for cells that are CD49f<sup>+</sup> and bind to an anti-CD49f antibody selected from the group consisting of monoclonal antibody GoH3 and

monoclonal antibody 4F10, to produce a population enriched for pancreatic stem cells, progenitors, or combinations thereof, wherein the selecting is by attachment to and disattachment from solid phase

- 5      22.      An antibody that specifically binds to the CD49f antigen, wherein said CD49f antigen specifically binds to the monoclonal antibody GoH3 or to the monoclonal antibody 4F10.
23.      The antibody of claim 22, wherein said antibody is a monoclonal antibody produced by a hybridoma cell line.
- 10      24.      The antibody according to claim 23, wherein said monoclonal antibody binds to the CD49f antigen as detected by the GoH3 antibody or the 4F10 antibody.
25.      An antibody that specifically binds to the CD133 antigen, wherein said CD133 antigen specifically binds to the monoclonal antibody AC133.
- 15      26.      The antibody of claim 25, wherein said antibody is a monoclonal antibody produced by a hybridoma cell line.
- 20      27.      The antibody according to claim 26, wherein said monoclonal antibody binds to the CD133 antigen as detected by the AC133 antibody.
28.      A method for enriching for human pancreatic stem cells, progenitors, or a combination thereof, comprising:
- 25      a)      combining a population of pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells with a reagent that specifically binds to the CD133 antigen, the CD49f antigen or both the CD133 and CD49f antigens; and
- b)      selecting for those cells that bind to the reagent,
- 30      wherein the selected cells are enriched for pancreatic stem cells, progenitors, or a combination thereof, as compared to the population.

29. The method according to claim 28, wherein said reagent is at least one antibody.

30. A method for producing a population enriched for human pancreatic stem cells, progenitors, or a combination thereof, comprising selecting from pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells for those cells that express CD133 and bind to monoclonal antibody AC133, to produce a population enriched for pancreatic stem cells, progenitors, or a combination thereof.

31. A method for producing a population enriched for human pancreatic stem cells, progenitors, or a combination thereof, comprising selecting from pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells for those cells that express CD49f and bind to monoclonal antibody GoH3 or to monoclonal antibody 4F10, to produce a population enriched for pancreatic stem cells, progenitors, or a combination thereof.

32. The method of claim 31, wherein the antibody is monoclonal antibody GoH3.

33. The method of claim 31, wherein the antibody is monoclonal antibody 4F10.

34. The method of claim 30, wherein the antibody is monoclonal antibody AC133.

35. The method of claim 1, wherein the population containing pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells is obtained from a suspension culture, an adherent monolayer culture, a pancreatic explant, or a gastrointestinal explant.

36. The method of claim 1, wherein the population containing pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells is obtained from primary pancreatic tissue or from primary gastrointestinal tissue.

37. A method for producing a population enriched for human pancreatic stem cells, progenitors, or a combination thereof, wherein the population is obtained from primary pancreas tissues, the method comprising selecting from a population of pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells for cells that are CD133<sup>+</sup>, CD49f<sup>+</sup>, or CD133<sup>+</sup>CD49f<sup>+</sup> the method further comprising the steps of further enriching for pancreatic stem cells, progenitors, or a combination thereof, by further selecting for those cells that are CD34<sup>+</sup>, CD45<sup>-</sup>, or CD34<sup>+</sup>CD45<sup>-</sup>.
38. A method for isolating a pancreatic stem cell, comprising:
- a) selecting from a population of primary pancreas tissues, the method comprising selecting from a population of pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells for at least one selected cell that binds to a monoclonal antibody selected from the group consisting of: AC133, GoH3, and 4F10;
  - b) introducing at least one selected cell to a serum free culture medium containing one or more growth factors; and
  - c) proliferating the at least one selected cell in the culture medium.
39. The method of claim 38, wherein the population containing primary pancreas tissues, the method comprising selecting from a population of pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells is obtained from a suspension culture or an adherent culture.
40. The method of claim 38, wherein primary pancreas tissues, the method comprising selecting from a population of pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells is obtained from human fetal, neonatal, juvenile, adult pancreas tissue.
41. The method of claim 38, further comprising the steps of further enriching a population for pancreatic stem cells, progenitors, or a combination thereof, by

- d) contacting the selected cells with a second monoclonal antibody that binds to CD34 antigen or CD45 antigen; and
- e) removing those cells that are CD34<sup>+</sup>, CD45<sup>+</sup>, or CD34<sup>+</sup>CD45<sup>+</sup> from the population,

5 wherein the remaining cells in the population are enriched for pancreatic stem cells, progenitors, or a combination thereof.

42. The method of claim 38, wherein the primary pancreas tissues, the method comprising selecting from a population of pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells are contacted with a monoclonal antibody that binds to CD34 antigen or a monoclonal antibody that binds to CD45 antigen, and wherein the bound cells are removed prior to the contacting of step a).

43. A method of producing a population from pancreatic tissue enriched for human pancreatic lineage committed progenitor and mature cells, comprising:

- a) contacting pancreatic cells, pancreatic-derived cells, or gastrointestinal-derived cells with a monoclonal antibody that binds CD9; and
- b) selecting said primary pancreas tissues, the method comprising selecting from a population of pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells that bind to the monoclonal antibody;

wherein the selected CD9<sup>+</sup> cells are enriched for human pancreatic lineage committed progenitor or mature cells capable of differentiating into insulin<sup>+</sup>  $\beta$  cells.

44. The method of claim 43, further comprising the steps of further enriching a population from pancreatic tissue for human pancreatic lineage committed progenitor cells by

- c) contacting the selected cells with a second monoclonal antibody that binds CD15; and
- d) removing those cells that are CD15<sup>+</sup>,

wherein the remaining cells in the population are CD15<sup>-</sup> and are enriched for human pancreatic lineage committed progenitor cells capable of differentiating into insulin<sup>+</sup>  $\beta$  cells.



45. The method of claim 43, wherein the primary pancreas tissues, the method comprising selecting from a population of pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells are contacted with an anti-CD15 monoclonal antibody, and wherein the bound cells are removed prior to the contacting of step a).
46. A method for producing a population enriched for human pancreatic lineage committed progenitor cells, comprising selecting from a population of primary pancreas tissues, the method comprising selecting from a population of pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells for those cells that are  $CD49f^{++}CD9^{+}$  or  $CD133^{+}CD9^{+}$ .
47. A method for isolating a pancreatic stem cell from primary pancreatic tissues, comprising:
- a) selecting from a population of pancreatic cells, pancreatic-derived cells, or gastrointestinal-derived cells for cells that are  $CD133^{+}$ ,  $CD49f^{+}$ , or  $CD133^{+}CD49f^{+}$ ;
  - b) removing the cells that are  $CD15^{+}$  wherein the remaining cells are  $CD15^{-}$ ;
  - c) introducing the cells remaining after step b) to a serum-free culture medium containing one or more growth factors; and
  - d) proliferating the remaining cells in the culture medium.
48. A method for producing a population enriched for human pancreatic stem cells, wherein the population is obtained from primary tissues, the method comprising selecting from a population of pancreatic tissue, pancreatic cells, pancreatic-derived cells, or primary gastrointestinal tissue or gastrointestinal-derived cells that are  $CD133^{+}$ ,  $CD49f^{+}$ , or  $CD133^{+}CD49f^{+}$  the method further comprising the steps of further enriching for pancreatic stem cells, by further selecting for those cells that are  $CD15^{-}$ .
49. A pancreatic stem cell, wherein the pancreatic stem cell is  $CD133^{+}CD49f^{+}$ .

50. A pancreatic progenitor cell committed to the endocrine  $\beta$ -cell lineage, wherein the progenitor cell is CD49f<sup>+</sup>CD9<sup>+</sup>.
51. The endocrine  $\beta$ -cell lineage committed pancreatic progenitor cell of claim 50, wherein  
5 the progenitor cell is also CD15<sup>-</sup>.
52. A pancreatic progenitor cell committed to the endocrine  $\beta$ -cell lineage, wherein the  
10 progenitor cell is CD49f<sup>+</sup>.